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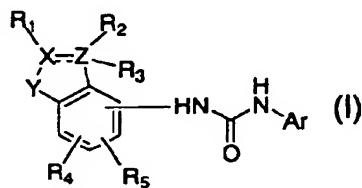
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(54) BIARYLUREA DERIVATIVES

(57) The present invention relates to a compound of Formula (I) and the manufacturing method(s) thereof and the use thereof:

Formula (I)



,wherein: Ar is a nitrogen-containing heteroaromatic ring group; X and Z are each a carbon atom, and so on; Y is CO, and so on; R₁ is a hydrogen atom, and so on; R₂ and R₃ are each a hydrogen atom, and so on; R₄ and R₅ are each a hydrogen atom, and so on; and the formula --- is a single bond or a double bond.

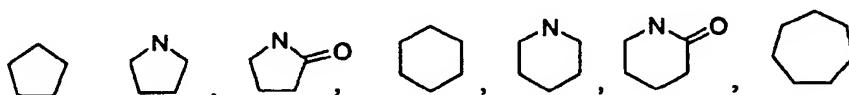
According to the present invention, the compound of the present invention can provide Cdk4 and/or Cdk6 inhibitors for treating malignant tumors, because the compounds of the present invention exhibit a prominent growth inhibitory activity against tumor cells.

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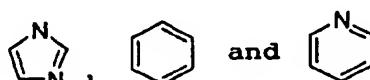
5 ; W₁ is a single bond, an oxygen atom, a sulfur atom, SO, SO₂, NR_q, SO₂NR_q, N(R_q)SO₂NR_r, N(R_q)SO₂, CH(OR_q), CONR_q, N(R_q)CO, N(R_q)CONR_r, N(R_q)COO, N(R_q)CSO, N(R_q)COS, C(R_q)=CR_r, C=C, CO, CS, OC(O), OC(O)NR_q, OC(S)NR_q, SC(O), SC(O)NR_q and C(O)O (wherein: R_q and R_r are respectively a substituent selected from a set of groups of (i) a hydrogen atom, (ii) a substituent selected from a set of groups consisting of a lower alkyl group, a cyclo lower alkyl group, a hydroxyl group, a cyano group, halogen atoms, a nitro group, a carboxyl group, a carbamoyl group, a formyl group, a lower alkanoyl group, a lower alkanoyloxy group, a hydroxy lower alkyl group, a cyano lower alkyl group, a halo lower alkyl group, a carboxy lower alkyl group, a carbamoyl lower alkyl group, lower alkoxy group, a lower alkoxy carbonyl group, lower alkoxy carbonylamino group, a lower alkoxy carbonylamino lower alkyl group, a lower alkyl carbamoyl group, a di-lower alkyl carbamoyl group, a carbamoyloxy group, a lower alkyl carbamoyloxy group, di-lower alkyl carbamoyloxy group, an amino group, a lower alkylamino group, a di-lower alkylamino group, a tri-lower alkylammonio group, an amino lower alkyl group, a lower alkylamino lower alkyl group, a di-lower alkylamino lower alkyl group, a tri-lower alkylammonio lower alkyl group, a lower alkanoylamino group, an aroylamino group, a lower alkanoylamidino lower alkyl group, a lower alkylsulfinyl group, a lower alkylsulfonyl group, a lower alkylsulfonylamino group, a hydroxyimino group and a lower alkoxyimino group, or (iii) a lower alkyl group, an aryl group or an aralkyl group which may be substituted with one to three of said substituent(s).); Y₁ and Y₂ are each, the same or different, a single bond or a straight-chain or branched lower alkylene group which may have a said bicyclic or tricyclic fused ring);

10 (2) may have a five- to seven-membered fused ring selected from a set of groups consisting of:

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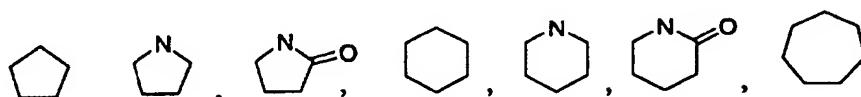


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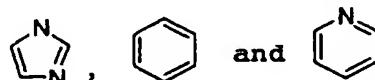
35 which may be formed together with the carbon atom of said nitrogen-containing heteroaromatic ring group, on which the substituent, which is selected from a set of groups consisting of a lower alkyl group, a lower alkanoyl group, a lower alkanoyloxy group, a hydroxy lower alkyl group, a cyano lower alkyl group, a halo lower alkyl group, a carboxy lower alkyl group, a carbamoyl lower alkyl group, lower alkoxy group, a lower alkoxy carbonyl group, lower alkoxy carbonylamino group, a lower alkoxy carbonylamino lower alkyl group, a lower alkyl carbamoyl group, a di-lower alkyl carbamoyl group, a carbamoyloxy group, a lower alkyl carbamoyloxy group, di-lower alkyl carbamoyloxy group, an amino group, a lower alkylamino group, a di-lower alkylamino group, a tri-lower alkylammonio group, an amino lower alkyl group, a lower alkanoylamino group, a lower alkylsulfinyl group, a lower alkylsulfonyl group, a lower alkylsulfonylamino group, a lower alkanoylamidino lower alkyl group (hereinafter indicated as ring-substituent) stands, the carbon atom next to said carbon atom, and a carbon atom, an oxygen atom and/or a nitrogen atom on said ring-substituent; or,

40 (3) may have a five- to seven-membered ring selected from a set of groups consisting of:

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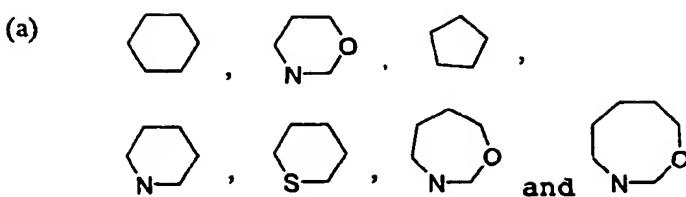


55 which may be formed together with the carbon atom of said nitrogen-containing heteroaromatic ring group on

which a substituent represented by the formula $Y_1-W_1-Y_2-R_p$ (wherein: Y_1 , W_1 , Y_2 and R_p have the same meanings as stated above) stands, the carbon atom next to said carbon atom, and a carbon atom, an oxygen atom and/or a nitrogen atom on said ring-substituent.

; X and Z are each, the same or different, a carbon atom or a nitrogen atom, or being taken together with R_1 or R_2 and/or R_3 which may exist on X or Z , form a CH or a nitrogen atom; Y is CO, SO or SO_2 ; R_1 is any of a hydrogen atom or a substituent represented by a formula $Y_3-W_2-Y_4-R_s$ (wherein: R_s is any of a hydrogen atom or a lower alkyl group, a lower alkenyl group, a lower alkynyl group, a cyclo lower alkyl group, an aryl group, and a heteroaromatic ring group selected from a set of groups consisting of an imidazolyl group, an isoxazolyl group, an isoquinolyl group, an isoindolyl group, an indazolyl group, an indolyl group, an indolizinyl group, an isothiazolyl group, an ethylenedioxyphenyl group, an oxazolyl group, a pyridyl group, a pyradinyl group, a pyrimidinyl group, a pyridazinyl group, a pyrazolyl group, a quinoxalinyl group, a quinolyl group, a dihydroisoindolyl group, a dihydroindolyl group, a thionaphthalenyl group, a naphthyridinyl group, a phenazinyl group, a benzoimidazolyl group, a benzoxazolyl group, a benzothiazolyl group, a benzotriazolyl group, a benzofuranyl group, a thiazolyl group, a thiadiazolyl group, a thiienyl group, a pyrrolyl group, a furyl group, a furazanyl group, a triazolyl group, a benzodioxanyl group and a methylenedioxyphenyl group, or an aliphatic heterocyclic group selected from a set of groups comprising an isoxazolinyl group, an isoxazolidinyl group, a tetrahydropyridyl group, an imidazolidinyl group, a tetrahydrofuran group, a piperazinyl group, a piperidinyl group, a pyrrolidinyl group, pyrrolinyl group, a morpholino group, a tetrahydroquinolinyl group and a tetrahydroisoquinolinyl group, all of which may be substituted with one to three of said substituent(s); W_2 is a single bond, an oxygen atom, a sulfur atom, SO , SO_2 , NR_t , SO_2NR_t , $N(R_t)SO_2NR_u$, $N(R_t)SO_2$, $CH(OR_t)$, $CONR_t$, $N(R_t)CO$, $N(R_t)CONR_u$, $N(R_t)COO$, $N(R_t)CSO$, $N(R_t)COS$, $C(R_v)=CR_r$, $C\equiv C$, CO , CS , $OC(O)$, $OC(O)NR_t$, $OC(S)NR_t$, $SC(O)$, $SC(O)NR_t$ and $C(O)O$ (wherein: R_t and R_u are each a hydrogen atom or a substituent selected from a set of groups consisting of a lower alkyl group, a hydroxy group, a cyano group, halogen atoms, a nitro group, a carboxyl group, a carbamoyl group, a formyl group, a lower alkanoyl group, a lower alkanoyloxy group, a hydroxy lower alkyl group, a cyano lower alkyl group, a halo lower alkyl group, a carboxy lower alkyl group, a carbamoyl lower alkyl group, lower alkoxy group, a lower alkoxy carbonyl group, a lower alkoxy carbonylamino group, a lower alkoxy carbonyl amino lower alkyl group, a lower alkyl carbamoyl group, a di-lower alkyl carbamoyl group, a carbamoyloxy group, a lower alkyl carbamoyloxy group, a di-lower alkyl carbamoyloxy group, an amino group, a lower alkylamino group, a di-lower alkylamino group, a tri-lower alkylammonio group, an amino lower alkyl group, a lower alkylamino lower alkyl group, a di-lower alkylamino lower alkyl group, a tri-lower alkylammonio lower alkyl group, a lower alkanoylamino group, a lower alkanoylamino lower alkyl group, an aroylamino group, a lower alkanoylamidino lower alkyl group, a lower alkylsulfanyl group, a lower alkylsulfonyl group, a lower alkylsulfonylamino group, a hydroxyimino group and a lower alkoxyimino group, or a lower alkyl group, an aryl group or an aralkyl group which may be substituted with one to three of said substituent(s)); Y_3 and Y_4 are each, the same or different, a single bond or a straight-chain or branched lower alkylene group), or an lower alkyl group which may be substituted with one to three of the same or different substituent(s) selected from a set of groups consisting of a lower alkyl group, a hydroxyl group, a cyano group, halogen atoms, a nitro group, a carboxyl group, a carbamoyl group, a formyl group, a lower alkanoyl group, a lower alkanoyloxy group, a hydroxy lower alkyl group, a cyano lower alkyl group, a halo lower alkyl group, a carboxy lower alkyl group, a carbamoyl lower alkyl group, lower alkoxy group, a lower alkoxy carbonyl group, lower alkoxy carbonylamino group, a lower alkoxy carbonyl amino lower alkyl group, a lower alkyl carbamoyl group, a di-lower alkyl carbamoyl group, a carbamoyloxy group, a lower alkyl carbamoyloxy group, di-lower alkyl carbamoyloxy group, an amino group, a lower alkylamino group, a di-lower alkylamino group, a tri-lower alkylammonio group, an amino lower alkyl group, a lower alkylamino lower alkyl group, a di-lower alkylamino lower alkyl group, a tri-lower alkylammonio lower alkyl group, a lower alkanoylamino group, a lower alkanoylamino lower alkyl group, an aroylamino group, a lower alkanoylamidino lower alkyl group, a lower alkylsulfanyl group, a lower alkylsulfonyl group, a lower alkylsulfonylamino group, a hydroxyimino group and a lower alkoxyimino group, or a substituent selected from a set of groups represented by the formula $Y_3-W_2-Y_4-R_s$ (wherein: R_s , W_2 , Y_3 and Y_4 have the same meanings as stated above), or forms a nitrogen atom, together with X); R_2 and R_3 are each independently, the same or different, a hydrogen atom, a hydroxy group, a lower alkyl group, a lower alkoxy group, or a substituent represented by the formula $Y_3-W_2-Y_4-R_s$ (wherein: R_s , W_2 , Y_3 and Y_4 have the same meanings as stated above), or either R_2 or R_3 forms, together with R_1 and X , a saturated five- to eight-membered cyclic group selected from sets of groups of (a) and (b):

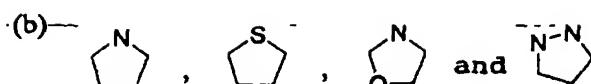
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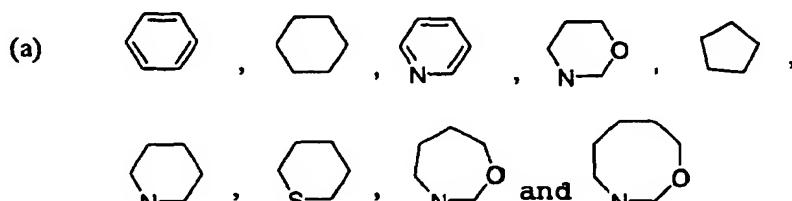
and

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and the other one of R_2 or R_3 binds to a carbon atom or a nitrogen atom on the ring, or to a carbon atom, an oxygen atom and/or a nitrogen atom on said ring-substituent of said ring to form a five- to seven-membered ring, or R_2 and R_3 are combined to form a spiro cyclo lower alkyl group, or are combined with Z on which they exist to form an oxo (keto, or carbonyl) group, or they (R_2 and R_3) form, together with Z , R_1 and X to which they bind, a saturated or an unsaturated five- to eight membered cyclic group which may be selected from sets of groups of (a) and (b):

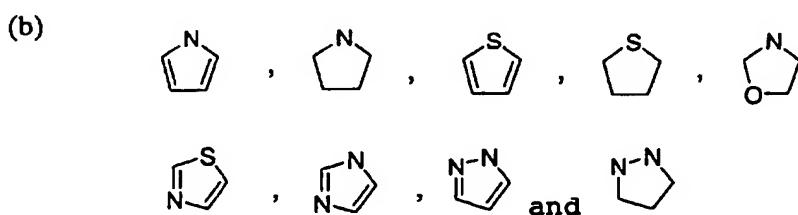
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and

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, which may contain one or more kinds of hetero atom(s) selected from the group of a nitrogen atom, an oxygen atom and a sulfur atom, or may be condensed with any of a cyclo lower alkyl group, an aryl group, a heteroaromatic ring group selected from a set of groups consisting of an imidazolyl group, an isoxazolyl group, an isoquinolyl group, an isoindolyl group, an indazolyl group, an indolyl group, an indolodinyl group, an isothiazolyl group, an ethylenedioxyphenyl group, an oxazolyl group, a pyridyl group, a pyradinyl group, a pyrimidinyl group, a pyridazinyl group, a pyrazolyl group, a quinoxalinyl group, a quinolyl group, a dihydroisoindolyl group, a dihydroindolyl group, a thionaphthalenyl group, a naphthyridinyl group, a phenazinyl group, a benzoimidazolyl group, a benzoxazolyl group, a benzothiazolyl group, a benzotriazolyl group, a benzofuranyl group, a thiazolyl group, a thiadiazolyl group, a thiienyl group, a pyrrolyl group, a furyl group, a furazanyl group, a triazolyl group, a benzodioxanyl group and a methylenedioxyphenyl group, or an aliphatic heterocyclic group(s) selected from a set of groups comprising an isoxazolinyl group, an isoxazolidinyl group, a tetrahydropyridyl group, an imidazolidinyl group, a tetrahydrofuranyl

group, a tetrahydropyranyl group, a piperazinyl group, a piperidinyl group, a pyrrolidinyl group, a morpholino group, a tetrahydroquinolinyl group and a tetrahydroisoquinolinyl group, which may be substituted with one to three of the same or different substituent(s) selected from a set of groups consisting of a lower alkyl group, a spiro cyclo lower alkyl group which may be substituted, a hydroxyl group, a cyano group, halogen atoms, a nitro group, a carboxyl group, a carbamoyl group, a formyl group, a lower alkanoyl group, a lower alkanoyloxy group, a hydroxy lower alkyl group, a cyano lower alkyl group, a halo lower alkyl group, a carboxy lower alkyl group, a carbamoyl lower alkyl group, lower alkoxy carbonyl group, lower alkoxy carbonylamino group, a lower alkoxy carbonylamino lower alkyl group, a lower alkyl carbamoyl group, a di-lower alkyl carbamoyl group, a carbamoyloxy group, a lower alkyl carbamoyloxy group, di-lower alkyl carbamoyloxy group, an amino group, a lower alkylamino group, a di-lower alkylamino group, a tri-lower alkylammonio group, an amino lower alkyl group, a lower alkylamino lower alkyl group, a di-lower alkylamino lower alkyl group, a tri-lower alkylammonio lower alkyl group, a lower alkanoylamino group, an aroylamino group, a lower alkanoylamidino lower alkyl group, a lower alkylsulfinyl group, a lower alkylsulfonyl group, a lower alkylsulfonylamino group, a hydroxyimino group and a lower alkoxyimino group, and a substituent selected from a set of groups represented by the formula $Y_1-W_1-Y_2-R_p$ (wherein: R_p , W_1 , Y_1 and Y_2 have the same meanings as stated above); R_4 and R_5 are each, the same or different, a hydrogen atom, halogen atoms, a hydroxy group, an amino group, or a substituent represented by the formula $Y_3-W_2-Y_4-R_s$ (wherein: R_s , W_2 , Y_3 and Y_4 have the same meanings as stated above), or any of a lower alkyl group, an aryl group or an aralkyl group which may be substituted with one to three of the same or different substituent(s) selected from both a set of groups consisting of a lower alkyl group, a cyano group, a nitro group, a carboxyl group, a carbamoyl group, a formyl group, a lower alkanoyl group, a lower alkanoyloxy group, a hydroxy lower alkyl group, a cyano lower alkyl group, a halo lower alkyl group, a carboxy lower alkyl group, a carbamoyl lower alkyl group, lower alkoxy group, a lower alkoxy carbonyl group, lower alkoxy carbonylamino group, a lower alkoxy carbonylamino lower alkyl group, a lower alkyl carbamoyl group, a di-lower alkyl carbamoyl group, a carbamoyloxy group, a lower alkyl carbamoyloxy group, di-lower alkyl carbamoyloxy group, an amino group, a lower alkylamino group, a di-lower alkylamino group, a tri-lower alkylammonio group, an amino lower alkyl group, a lower alkylamino lower alkyl group, a di-lower alkylamino lower alkyl group, a tri-lower alkylammonio lower alkyl group, a lower alkanoylamino group, an arylamino group, a lower alkanoylamidino lower alkyl group, a lower alkylsulfinyl group, a lower alkylsulfonyl group, a lower alkylsulfonylamino group, a hydroxyimino group and a lower alkoxyimino group, and a set of groups represented by the formula $Y_3-W_2-Y_4-R_s$ (wherein: R_s , W_2 , Y_3 and Y_4 have the same meanings as stated above); and the formula -- represents either a single bond or a double bond.

[0021] Symbols and terms described in this specification are to be explained as follows.

[0022] "Nitrogen-containing heteroaromatic ring group" is an aromatic ring group which has at least one nitrogen atom, and also an aromatic ring group which has one or more hetero atoms selected from a group consisting of an oxygen atom and a sulfur atom other than the above-mentioned nitrogen atom. As specific examples of such groups, there may be mentioned, for example, a pyridyl group, a pyrimidinyl group, a pyradinyl group, a pyridazinyl group, a thiazolyl, a isothiazolyl, a oxazolyl, a isoxazolyl, a pyrazolyl group, a pyrrolyl group, an imidazolyl, a indolyl, a isoindolyl, a quinolyl group, a isoquinolyl, a benzothiazolyl group or a benzoxazolyl group. Among them, a pyridyl group, a pyrimidinyl group, a pyradinyl group, a pyridazinyl group, a thiazolyl, a pyrazolyl group, or an imidazolyl group are more preferable, and a pyridyl group and a pyrazolyl group are especially preferable.

[0023] As a lower alkyl group, a straight-chain or branched chain alkyl group with one to six carbon atoms such as a methyl group, an ethyl group, a propyl group, an isopropyl group, a butyl group, an isobutyl group, a sec-butyl group, a tert-butyl group, a pentyl group and a hexyl group is preferable. Among them, a methyl group, an ethyl group and a butyl group are more preferably employed.

[0024] As halogen atoms, there may be mentioned, for example, a fluorine atom, a chlorine atom, a bromine atom and an iodine atom, more preferably, among them, a fluorine atom and a chlorine atom, and so on.

[0025] As a lower alkanoyl group, preferable is a group which may be formed by substituting a carbonyl group with an alkyl group which consists of one to five carbon atoms. As specific examples of such groups, there may be mentioned an acetyl group, a propionyl group, a butyryl group, an isobutyryl group, a valeryl group, and an isovaleryl group, a pivaloyl group and a pentanoyl group. Among them, for example, an acetyl group and a propionyl group and a pivaloyl group are more preferable.

[0026] A lower alkanoyloxy group is a group where an oxygen atom is substituted with the lower alkanoyl group stated above. As specific examples of such groups, there may be mentioned an acetoxy group, a propionyloxy group, a butyryloxy group, an isobutyryloxy group, a valeryloxy group, and an isovaleryloxy group, a pivaloyloxy group and a pentanoyloxy group, and so on. Among them, for example, an acetoxy group and a propionyloxy group and a pivaloyloxy group are more preferable.

[0027] As a hydroxy lower alkyl group, preferable is an alkyl group with one to six carbon atoms substituted with hydroxyl group. Specific examples are, for example, a hydroxymethyl group, a dihydroxymethyl group, a trihydroxyme-